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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,977	03/31/2004	William S. Dynan	791301-1010	6138

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/813,977	DYNAN ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,9,11-13,15-17,19,27-32 and 34-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *27-31* is/are allowed.

6)☒ Claim(s) *1-6,8,9,11-13,15-17,19,32 and 34-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 2/18/07 in response to the Office Action of 10/17/06 are acknowledged and have been entered.

Claims 1-6, 8, 9, 11-13, 15-17, 19, 27-32, and 34-39 are pending.

Claims 1 and 37 have been amended by Applicant.

Claims 1-6, 8, 9, 11-13, 15-17, 19, 27-32, and 34-39 are currently under examination.

The following Office Action contains NEW GROUNDS of rejections based on new considerations.

Rejections Withdrawn

All rejections found in the Office Action of 10/17/06 are withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 8, 9, 11-13, 15-17, 19, and 37-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to "pharmaceutical" compositions comprising the polypeptide sequence set-forth in SEQ ID NO:17 and "pharmaceutical" compositions comprising single chain antibodies that bind to a polypeptide sequence comprising SEQ ID NO:16 or a portion thereof and inhibits non-homologous end-joining.

The term "pharmaceutical" indicates that the claimed compounds have therapeutic properties in vivo; however, the specification lacks working examples demonstrating that the claimed compounds predictably have therapeutic effects in vivo.

Therapeutic treatments, in general, are unpredictable as underscored by Gura (Science, 1997, 278:1041-1042.) who discusses the potential shortcoming of potential

anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with cologenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041 first column, in particular) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

The specification have provided in vitro examples (Examples 2, 4, 6, and 8); however, those of ordinary skill in the art recognize that treatment in vivo is not predictive. The instant situation is analogous to that of *In re* Brana (34 U.S.P.Q. 2d 1436, 1440 (Fed. Cir. 1995)). A review of *In re Brana* reveals an application that claimed a chemical compound for treating a cancer, wherein the chemical compound was structurally similar to known compounds that have known in vivo use to treat tumors, and more importantly, Applicant provided in vivo data that the claimed compound could treat tumors in mice, hence it was ruled that the claimed compound was enabled for treating tumors. In the instant application, the claims are not drawn to products which have known in vivo ability to give rise to a therapeutic effect. Further, the instant specification provides no in vivo data, particularly demonstrating that the claimed products would predictably give rise to a therapeutic effect in vivo. In view of *In re Brana*, Examiner asserts that successful use of in vivo mouse models enables compositions for specific therapeutic effects in humans and does not require human clinical testing; however, the instant application is claiming a product that provides a

therapeutic effect without providing any in vivo data, hence the claimed invention is not enabled. All of this underscores the criticality of providing workable examples which are not disclosed in the specification, particularly in an unpredictable art, such as pharmaceuticals.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the product would function as claimed.

It is noted that the anticipation rejections, below, are based on the structural requirements recited in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Carter et al (Mol. and Cell. Biol., 1990, 10(12):6460-6471), as *evidenced* by Li et al (Nucleic Acids Research, 2003, 31(20):5848-5857) and the specification.

Carter et al teaches a monoclonal antibody, mAb 18-2, which was used in the production of a single chain antibody taught by Li et al and described in the specification (see left column of page 5849 of Li et al and page 38 of the instant specification, in particular). As evidenced by the specification (page 19 lines 30-31 and page 18 lines

24-29, in particular), the single chain antibody evidenced by Li et al (generated from parental antibody mAb18-2, taught by Carter et al) comprises the CDRs encoded by instant SEQ ID NOs:18-23. Further, because the single chain antibody evidenced by Li et al was generated from the antibody taught by Carter et al, the antibody taught by Carter et al *inherently* has the same CDRs, in an immunoglobulin framework, as the single chain antibody evidenced by Li et al and the specification (CDRs encoded by instant SEQ ID NOs:18-23). Further, since the single chain antibody taught by Li et al binds SEQ ID NO:16 (see page 43 lines 12-15 and page 39 lines 17-22 of the specification, in particular), mAb 18-2 and the single chain antibody taught by Li et al have identical CDRs, and Western blot analysis of mAb 18-2 and the single chain antibody taught by Li et al demonstrate identical binding to DNA-PKcs (as evidenced by Figure 1C of Li et al), the antibody taught by Carter et al would bind SEQ ID NO:16, which is found on regions outside of the catalytic domain of DNA-PKcs. Further, as evidenced by Li et al (page 5850 right column, in particular), mAb 18-25 inhibits less than about 50% of DNA-PKcs enzymatic activity. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not perform the same function as the claimed product. In the absence of evidence to the contrary, the burden is on Applicant to prove that this function of the claimed product is different from that taught by the prior art and to establish patentable differences. See In re Best 562F .2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2nd 1992 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 5, 32, and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter et al (Mol. and Cell. Biol., 1990, 10(12):6460-6471) as applied to claims 1, 2, 4, and 5 above, and further in view of Bejcek et al (Cancer Research, 1995, 55:2346-2351) and Schwarze et al (Science 9/3/99, 285:1569-1572).

Anticipation of claims 1, 2, 4, and 5 by Carter et al is described above. Carter et al does not specifically teach a single chain antibody comprising a protein transduction domain wherein the single chain antibody inhibits DNA repair by binding to a repair polypeptide and includes the CDR regions SEQ ID NOs:18-23 in an immunoglobulin framework. (claim 32), wherein the DNA repair polypeptide comprises DNA-PKcs (claim

34), wherein the single chain antibody binds to a region including SEQ ID NO:16 or a potion thereof (claims 35-36) and inhibits non-homologous end joining (claim 37). However, these deficiencies are made up in the teachings of Bejcek et al and Schwarze et al.

Bejcek et al teaches single chain antibodies constructed from mAbs (pages 2346-2347, in particular). Bejcek et al further teaches single chain antibodies overcome several problems associated with intact mAbs, particularly because of the large size of the mAbs and the resultant relative inability to penetrate tissue (page 2350, in particular).

Schwarze et al teaches delivery of proteins into cells by adding a protein transduction domain to said proteins (right column of page 1570, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to produce a single chain antibody comprising the CDRs of the antibody taught by Carter et al (CDR regions SEQ ID NOs:18-23) in an immunoglobulin framework attached to a protein transduction domain because the target of the antibody taught by Carter et al is inside cells (see pages 642-643 of Carter et al) and Bejcek et al teaches single chain antibodies constructed from mAbs penetrate tissue better than intact mAbs (page 2350, in particular) and Schwarze et al teaches adding a protein transduction domain to proteins enhances said protein's ability to enter cells (right column of page 1570, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for producing a single chain antibody comprising the CDRs of the antibody taught by Carter et al

(CDR regions SEQ ID NOs:18-23) in an immunoglobulin framework attached to a protein transduction domain because Bejcek et al teaches single chain antibodies constructed from mAbs (pages 2346-2347, in particular) and Schwarze et al teaches adding a protein transduction domain to said protein (right column of page 1570, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results. Further, since the single chain antibody taught by Li et al binds SEQ ID NO:16 (see page 43 lines 12-15 and page 39 lines 17-22 of the specification, in particular), mAb 18-2 and the single chain antibody taught by Li et al have identical CDRs, and Western blot analysis of mAb 18-2 and the single chain antibody taught by Li et al demonstrate identical binding to DNA-PKcs (as evidenced by Figure 1C of Li et al), the single chain antibody taught by the combined teachings of Carter et al, Bejcek et al, and Schwarze et al would bind SEQ ID NO:16, which is found on regions outside of the catalytic domain of DNA-PKcs. Further, as evidenced by Li et al (page 5850 right column, in particular), mAb 18-2 inhibits less than about 50% of DNA-PKcs enzymatic activity. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not perform the same function as the claimed product. In the absence of evidence to the contrary, the burden is on Applicant to prove that this function of the claimed product is different from that taught by the prior art and to establish patentable differences. See In re Best 562F .2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2nd 1992 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

Claims 1, 2, 4, 5, 32, and 34-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter et al (Mol. and Cell. Biol., 1990, 10(12):6460-6471) in view of Bejcek et al (Cancer Research, 1995, 55:2346-2351) and Schwarze et al (Science 9/3/99, 285:1569-1572). as applied to claims 1, 2, 4, 5, 32, and 34-37 above, and further in view of Kelley et al (US Patent 6,252,048 B1; 6/26/01) or Jang et al (Molecular Breeding, 2002, 9:81-91).

Anticipation of claims 1, 2, 4, 5, 32, and 34-37 by the combined teachings of Carter et al, Bejcek et al, and Schwarze et al is described above.

The combined teachings of Carter et al, Bejcek et al, and Schwarze et al does not specifically teach single chain antibodies comprising nuclear localization signals or chloroplast localization signals. However, these deficiencies are made up in the teachings of Kelley et al and Jang et al.

Kelley et al teaches a nuclear localization signal that was recombinantly added to a DNA repair protein to improve the nuclear localization of the protein (column 62 lines 25-28, in particular).

Jang et al teaches a protein comprised of a chloroplast localization signal (pages 82-83, in particular). Jang et al further teaches that adding a chloroplast localization signal to polynucleotide constructs expressed in plants enhances expression of the protein product (page 87-88 and Figure 5, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to add a nuclear localization signal to the single chain antibody taught by the combined teachings of Carter et al, Bejcek et al, and Schwarze et al because Kelley et al teaches nuclear localization signals send protein constructs to the nucleus (column 62 lines 25-28, in particular) and Carter et al teaches the target of the single chain antibody is found in the nucleus (see abstract, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for adding a nuclear localization signal to the single chain antibody taught by the combined teachings of Carter et al, Bejcek et al, and Schwarze et al because Kelley et al teaches adding nuclear localization signals to protein constructs (column 62 lines 25-28, in particular).

Further, one of ordinary skill in the art at the time the invention was made would have been motivated to add a chloroplast localization signal to the single chain antibody taught by the combined teachings of Carter et al, Bejcek et al, and Schwarze et al because Jang et al further teaches that adding a chloroplast localization signal to polynucleotide constructs expressed in plants enhances expression of the protein product (page 87-88 and Figure 5, in particular) and one of skill in the art would recognize that enhanced production of the single chain antibody would enable one of skill to perform more assays with said antibody. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for adding a chloroplast localization signal to the single chain antibody taught by the combined teachings of Carter et al, Bejcek et al, and Schwarze et al because Jang et al

teaches adding chloroplast localization signals to protein constructs (pages 82-83, in particular).

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Summary

Claims 27-31 appear allowable. Claims 1-6, 8, 9, 11-13, 15-17, 19, 32, and 34-39 are rejected under 35 U.S.C. 102, 35 U.S.C. 103, and/or are rejected under 35 U.S.C. 112, first paragraph.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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